



Evaluation of *Ocimum gratissimum* Leaf Extract on Lipid Profile of Experimentally-Induced Prostatic Hyperplasia Animal Model

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MNU and MAM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MNU and MUE managed the analyses of the study. Authors MNU and MUE managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Benign Prostate hyperplasia (BPH) is a highly prevalent disease among older men and a substantial public health problem. We investigated leaf extract of *Ocimum gratissimum* (OG) effect on lipid prolife in BPH.

Methods: BPH was induced in male rats weighing 200-300g through exogenous administration of testosterone and estradiol. Thirty (30) rats were divided into five groups. Four groups received subcutaneous injections of the two hormones and one group was used as a control with injections of hormones. Groups I to II were administered orally with different doses of extract and group III received standard drug, group IV was not treated and group V served as normal control. After Thirty-five days of treatment, the rats were sacrificed and blood collected through cardiac puncture for biochemical analysis. The prostate were harvested and weighed.

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Results: In rats treated with extract and standard drug a significant decrease in the size of the enlarged prostate was observed ($P<0.05$) when compared with the BPH control group. Weight gain was observed in rats treated with extract and finasteride. The level of cholesterol, LDL-C and VLDL-C were significantly reduced while HDL-C increased when compared to the BPH control.

Conclusion: The significant reduction of cholesterol, LDL, VLDL-C and increase in HDL-C in the treated groups supported by decline in prostate weight suggest that the extract have the capacity of managing the lipid alterations caused by induction of BPH in rats.

Keywords: Testosterone; estradiol; lipoprotein; prostate; *Ocimum gratissimum*.

1. INTRODUCTION

Benign Prostate hyperplasia (BPH) is a common disease in the aging men and causes substantial adverse health effects. BPH, leading to enlargement of the prostate and in turn resulting in lower urinary tract symptoms (LUTS), has high prevalence and socio-economic burden [1,2,3]. Therefore, it is important to determine the risk factors of BPH progression and to keep men away from them. However limited data are available concerning factors that might be protective against the development of BPH. Recently a growing amount of researches demonstrated that metabolic syndrome (MS) and/or its individual components are involved in the development and progression of BPH [4,5, 6]. The individual components of MS, including insulin resistance [7], dyslipidemia [8], obesity [9], hypertension [10] and the syndrome itself might predispose patients to greater risks of BPH and LUTS.

Available data indicate that BPH patients have higher total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels and lower high-density lipoprotein cholesterol (HDL-C) levels compared with non-BPH patients [11]. Furthermore several reports suggested that BPH is one of components of MS [12]. With the accumulation of knowledge about MS and BPH, it has been known that insulin resistance (IR) is the cornerstone of MS and play a critical role in the growth of prostate and the progression of BPH [13,14]. In addition to IR, inflammation and oxidative stress were reported to be involved in the development and progression of BPH [15, 16,17]. Despite the fact that the association between prostate diseases and MS is generally accepted, the pathogenetic link still needs to be deeply elucidated.

Scientific evaluation of medicinal plants is important to the discovery of novel drugs and also helps to assess toxicity risks associated with

the use of either herbal preparations or conventional drugs of plant origin.

Some studies have established the 5 α -reductase inhibitory activities of certain herbs such as *Ganoderma lucidum*, *Urtica dioica*, *Caesalpinia bonducella*, *Tribulus terrestris*, *Pedaliium murex*, *Sphaeranthus indicus*, *Cuscuta reflexa*, *Citrullus colocynthis*, *Benincasa hispida*, *Phyllanthus niruri*, *Echinops echinatus*, *Pygeum africanum* and *Hypoxis rooperi*, confirming that they are useful in the management of androgenic disorders which include BPH [1,2,18,19,20,21, 22,23]. Several studies have established the usefulness of herbal medicine in the management of BPH [2,20,24]. Previous reports on phytotherapeutic management of BPH established the inhibitory effect of *Lepidium meyeri* extract [25] and protective effect of *Echinops echinatus* and *Ganoderma lucidum* extracts [20,21] on testosterone induced BPH. *Benincasa hispida* Congn., *Sphaeranthus indicus*, *Abrus precatorious* and *Urtica dioica* were reported to inhibit 5-alpha reductase enzyme activity [1,26] and these plants have demonstrated ameliorative effect on testosterone-induced prostate hyperplasia by reducing relative prostate weight in treated animals [1,22,23]. *Serenoa repens* also known as saw palmetto contains sterols and its inhibitory effect on 5-alpha reductase activity with attendant decrease in DHT production has been reported to be useful in the management of [27]. Peng et al. [28] established that antrodan, a β -glucan obtained from *Antrodia cinnamomea mycelia*, is helpful in managing benign prostate hyperplasia.

Ocimum gratissimum contain different compounds such as alkaloids, saponins, tannins, anthraquinone, flavonoids, steroids, terpenoids and cardiac glycosides [29,30,31] which makes it useful in traditional medication. This study investigated the usefulness of the leaf extract of *Ocimum gratissimum* in the management of the

experimentally hormone-induced BPH in Wistar rats and its effect on lipid metabolism. The results will contribute to the search for locally available phytotherapeutic agents that can help in managing this debilitating disease especially in among the poor ones.

2. MATERIALS AND METHODS

2.1 Plant Material

Fresh leaves of *Ocimum gratissimum* were harvested from a garden in Okuku in Yala Local Government of Cross River State, South-South, Nigeria. The plant was identified and authenticated by Dr. Michael Eko, a botanist in the Department of Biological Sciences, University of Calabar and a voucher specimens number 431 deposited in a herbarium in the Department of Botany. Their fresh leaves were washed and dried under the shade for seven days. The dried leaves were pulverized using pestle and mortar to get a powder that was used for extraction.

2.1.1 Preparation of extract

The powdered sample of *Ocimum gratissimum* 200 g was soaked into 200 ml of distilled water, this was filtered after 48 hours and filtrate was concentrated in water bath. The solutions were diluted with corn oil, to produce a solution 100 mg/ml. The administration of extract was totally by gavage.

2.2 Hormones

Testosterone propionate Brand name: Ricostrone; a product of Greenfield pharma, Jiangsu Co Ltd., China. Estradiol valerate (by Medipharma Ltd., 108-Kotlakhpat industrial Est; Lahore, India. Testosterone propionate (T) and estradiol valerate E₂ (puregynon depot) were used for the induction of prostate enlargement at doses of 400 µg T and 80 µg E₂ [32] respectively. This was administered to the rats for three weeks subcutaneously in the inguinal region. All Chemicals used in this study were of analytical grade and were obtained from reputable companies.

2.3 Animals

A total of thirty (30) Wistar rats weighing between 200-300g were obtained from the animal house of the Faculty of Basic Medical Sciences, Cross River University of Technology, Okuku Campus,

Nigeria. The rats were used for the experiment. The rats were acclimatized for two weeks before the experiment commences. The rats were exposed to approximately 12-hour light/dark cycles under humid tropical conditions, given tap water and feed *ad libitum*, and were housed in standard plastic cages (five per cage) throughout the 35-day duration of the study. The animal room was well ventilated with a temperature range of 27-29°C. The Institutional Animal Ethics Committee, Cross River University of Technology, Calabar, Nigeria, (IAEC/CRUTECH/17/083) approved the study before the experiment and certified all experimental protocols.

2.3.1 Induction of BPH

BPH was induced by exogenous administration of testosterone and estradiol in staggered doses three times a week respectively for three weeks. The hormones were diluted with corn oil which served as the solvent. The dilution was done by taken 19 mL of corn oil and adding it to 1 mL (25 mg) of testosterone to form a 20 mL stock solution while 24 mL of corn oil was added to 1 mL of estradiol to make up a stock solution of 25 mL. From the stock solutions prepared, 200g rat was injected with 400 µg of testosterone and 80 µg of estradiol separately at the different thighs [32] with modification by Mbaka et al. [33].

2.3.2 Animal grouping and treatment

The animals were divided into five (5) groups each comprised of six (6) male rats. Four groups were induced with BPH which were grouped as group I to group IV). Groups I and II received 50 and 100 mg kg⁻¹ body weight (bw) of *Ocimum gratissimum* extract; group III received finasteride (orthodox drug) at 0.1 mg kg⁻¹; all by gavages for thirty five days, group IV was left untreated for thirty five days before sacrifice to assess possible reversal of the exogenous induction and group 5 served as normal control. The animals were weighed prior to the commencement of the experiment and subsequently every week till the end of the experiment.

Table 1. Animal grouping and treatment (Daily for 35 days)

Group	Treatment
I	BPH + 50 mg/kg OG
II	BPH + 100 mg/kg OG
III	BPH + 0.1 mg/kg of Finasteride
IV	BPH Control
V	Normal control

2.4 Determinations of Biochemical Parameters

After 35 days, the rats were anaesthetized by a brief exposure to trichloromethane vapour and bled by cardiac puncture. The sera were carefully separated and used for the determination of various biochemical analyses. Each rat's carcass was promptly dissected and the prostates were carefully excised. The prostates were freed of external fascias, washed in cold normal saline, blotted with filter paper and weighed on a sensitive balance.

2.4.1 Determination of total cholesterol, High density lipoprotein (HDL-cholesterol) and Triacylglycerol determination

Determination of total cholesterol, high density lipoprotein (CHOD-PAP method) as described by the National Cholesterol Education Program (NCEP) [34] while Triacylglycerol (GPO-PAP method) as described by Tietz [35]. Low density lipoprotein was determined as described by Assmann [36]. All were done using Randox assay kits.

2.5 Statistical Analysis

The experimental data were analysed for statistical significance by one-way analysis of variance and post hoc comparison using the SPSS version. All data were reported as mean $\pm$ SD and statistical significance was accepted at $P < 0.05$.

3. RESULTS

3.1 Effect of Extract of OG and Finasteride on Body Weight, Prostate Weight and Prostate/Body Weight Ratio

The effect of oral administration of extract and finasteride on body weight is shown in Table 2. The BPH-control group exhibited a decline in body weight when compared with normal control. The extract and standard drug (finasteride) treated groups exhibited an increase in body weight when compared with the BPH control group. Administration of extract or standard drug (finasteride) improved the body weight near normal level when compared with normal control.

The weight of the prostates and prostate/body weight ratio were at the highest in the BPH

control group when compared with normal control group (Table 2). BPH control group exhibited a significant ($P < 0.05$) increase in prostate weight and prostate/body weight ratio when compared to normal control. The extract and standard drug treated groups showed a decrease in prostate weight and prostate/body weight ratio when compared with the BPH-control group.

3.2 Lipid Profile

There was a significant ($P < 0.05$) rise in the serum cholesterol level in BPH control group when compared with the treated groups. In all the treated groups there was an improved reduction of serum cholesterol levels when compared to the BPH control group.

The results indicate that there was a significant reduction in the TG concentration in the OG treated and standard drug treated groups when compared the BPH control group. A significant ($P < 0.05$) decrease in the serum HDL-C level in BPH control group was observed when compared with the treated groups. In all the treated groups there was an increase in serum HDL-C concentrations when compared to the BPH control group.

There was a significant ($P < 0.05$) rise in LDL-C level of BPH control group when compared with the treated groups. Treatment with the extract showed a significant decline in the levels of LDL concentrations when compared to the BPH control (Table 3).

4. DISCUSSION

In the prostate gland, lipids promote the cellular proliferation, contractility and overall enlargement of the prostate and thus represent a potential risk factor for BPH and prostate cancer [37,38]. The prostate is a cholesterol-rich tissue; therefore elevated serum cholesterol may result in the accumulation of cholesterol in the cell membrane forming large lipid rafts [39]. These lipid rafts have been shown to have pro-carcinogenic cell signalling effects that will result in the enlargement of prostate.

Some data point out that modifiable risk factors of cardiovascular disease might raise the risk of BPH and contribute to its development. Obesity [7,40,41,42] elevated fasting plasma glucose levels [43,44] diabetes [10], and the metabolic syndrome, have been linked to cause an

Table 2. Effect of extract of OG and finasteride body weight, prostate weight and prostate/body weight ratio

Group	BW (g)	PW (mg)	P/BW ratio (mg/g)
BPH + 50 mg OG	254.30±7.22 ^b	700±300.00 ^{ab}	2.75±0.04 ^c
BPH + 100 mg OG	267.70±8.60 ^b	1000±400.00 ^b	3.74±0.05 ^c
BPH + Finasteride	270.30±7.98 ^c	530±220.00 ^{ab}	1.96±0.03 ^b
BPH control	220.30±7.92 ^a	2110±270.00 ^c	9.58±0.07 ^d
Normal control	272.10±7.90 ^c	310±60.00 ^a	1.14±0.1 ^a

Values are expressed as Mean ± SD. Benign prostate hyperplasia (BPH), *Ocimum gratissimum* (OG), Body weight (BW), Prostate weight (PW), Prostate/body weight (P/BW) ratio. Non- identical superscripts (i.e. a, b, c) means there is significance between the comparing groups at $P < 0.05$

Table 3. Effect of extract of OG and finasteride on serum lipid profile

Group	Cholesterol (mg/dl)	Triacylglycerol (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	VLDL-c (mg/dl)
BPH + 50 mg OG	147.70±3.93 ^{bcd}	70.00±1.20 ^b	59.78±3.18 ^a	12.27±3.93 ^{ab}	15.20±0.26 ^b
BPH + 100 mg OG	146.46±3.42 ^{bcd}	69.24±1.75 ^b	60.81±4.07 ^a	11.58±1.98 ^{ab}	15.05±0.37 ^b
BPH + Finasteride	155.00±6.93 ^{cd}	68.37±5.04 ^b	60.73±1.57 ^a	15.85±3.59 ^{bc}	14.88±1.03 ^b
BPH control	175.82±11.81 ^e	76.12±5.32 ^c	79.78±3.86 ^b	22.27±12.35 ^c	16.43±1.08 ^c
Normal control	131.78±4.89 ^a	61.37±1.52 ^a	63.32±1.64 ^a	7.35±2.69 ^a	13.48±0.32 ^a

Values are expressed as Mean ± SD. Benign prostate hyperplasia (BPH), High density lipoprotein (HDL), Low density lipoprotein (LDL), *Ocimum gratissimum* (OG). Identical superscript (i.e. a) means there is no significant difference between the comparing group $P > 0.05$. Non- identical superscripts (i.e. a, b, c, d, e) means there is significance between the comparing groups at $P < 0.05$

increased risk of BPH and male LUTS. Anomalous in concentrations of lipids and lipoproteins are well-proved risk factors for cardiovascular disease, and include elevated serum low density lipoprotein cholesterol, decreased serum high-density lipoprotein (HDL-c), and increased serum triglycerides. These factors make-up the metabolic syndrome and often arise in association with other cardiovascular risk factors, including diabetes. This observation raises the likelihood that abnormal lipids and lipoproteins might also be linked to the cause of BPH [45].

Some researchers [46] observed that prostate weight was significantly higher in hyperlipidemic rats than in controls. The increased prostate weight is used as one of crucial markers of BPH according to previous study [47,48]. BPH is characterized by stromal and epithelial cells hyperplasia, resulting in prostate enlargement. In previous studies, animals with BPH had a significant increase in prostate weight compared with normal control animals, whereas those of animals treated with finasteride or others herbal remedies for the management of BPH had significantly reduced the weight compared with BPH animals [47,49,50].

In a subsequent report, some researchers [51] observed that men with BPH had significantly

higher total cholesterol and low-density lipoprotein (LDL) cholesterol levels than did men without BPH. Obesity and dyslipidemia have been well reported to increase risk of BPH and high grad CaP [11,52].

The estimation of lipid profile indicated that the extract was capable of reducing the concentrations of cholesterol, triacylglycerol, low density lipoprotein and very low density lipoprotein in the treated rats. Some pervious researches indicated similar progression [3,53]. Total-cholesterol and low-density lipoprotein have been established to be significantly high in BPH patients compared to normal person [51]. It has been established that the amount of body fat found in males increases as one gets older [54]. It is likely that the increase amount of body fat as a result of increased age can join to increase the development and progression of BPH.

Increase in concentrations of cholesterol, triacylglycerol, low density lipoprotein and very low density lipoprotein and decrease in high density lipoprotein in BPH control group implies lipid metabolism is implicated in BPH condition. Treatment with extract was able to attenuate this alteration in lipid metabolism. It therefore means that reduction of the body fat is crucial in improving the management of BPH. This study indicates that *Ocimum gratissimum* has the

capacity to control the metabolism of lipid which can very helpful in the management of benign prostate hyperplasia.

5. CONCLUSION

The assessment of lipid profile indicated that the extract was capable of reducing the concentrations of cholesterol, triacylglycerol, low density lipoprotein and very low density lipoprotein in the treated rats. As it has been established, that lipids can promote cellular proliferation, contractility and overall enlargement of the prostate gland. It is therefore logical to suggest that reduction of lipid component of the body will go a long way in management of benign prostatic hyperplasia.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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